USSN 10/023,441
Attorney Docket CP216

DECLARATION OF MARTIN J. JACOBS UNDER 37 C.F.R. § 1.132

I, Martin J. Jacobs, hereby declare the following.

(1) I received my Bachelor of Science Degree in Chemistry from Illinois Institute of Technology 1969. I received my Doctor of Philosophy Degree in Organic Chemistry from Colorado State University in 1975.

(2) I have extensive experience in the formulation of pharmaceutical drug products for therapeutic use, including formulations involving modafinil.

(3) I am a Formulation Development Scientist in the Formulation Development Department of Cephalon, Inc., the assignee of the present application, and have been employed by Cephalon since July, 1999.

(4) I am a joint inventor of the subject matter claimed in the above-identified application, and generally speaking, claims 99-136 define methods of administering a modafinil compound complexed with a cyclodextrin.

(5) I am familiar with the Office Action dated November 21, 2005.

(6) I have studied the publication Loftsson, T. et al., *J. Pharm. Sci.*, **1996**, *85*, 1017-1025. In my opinion, Loftsson recognizes that the most common pharmaceutical application of cyclodextrins is to enhance aqueous drug solubility. However, Loftsson further recognizes that drug solubilization by cyclodextrins is largely unpredictable, but may be best for compounds of very low aqueous solubility:

> Although prediction of compound solubilization by cyclodextrins continues to be highly empirical, various historical observations permit several general statements. First, the lower the aqueous solubility of the pure drug, the greater the relative solubility enhancement obtained thorough cyclodextrin complexation. Drugs that possess aqueous solubility in the micromole/liter range generally demonstrate much greater enhancement than drugs possessing solubility in the micromole/liter range or higher. (p. 1020, col. 2).

Therefore, Loftsson teaches that predicting the aqueous solubility of a drug after cyclodextrin complexation is dependent upon the initial water solubility of the drug, and only drugs having an aqueous solubility in the micromole/L range (or lower) may be predicted to display large enhancements in aqueous solubility upon cyclodextrin complexation.

(7) As reported in the New Drug Application (NDA) for modafinil submitted to the Food and Drug Administration (FDA), the aqueous solubility of modafinil is 0.4 mg/mL. Given that the molecular weight of modafinil is 273.35 g/mol, the aqueous solubility of modafinil is 1.46 mmol/L, which is higher than the micromole/L range set forth in Loftsson. Accordingly, modafinil was not expected to exhibit a large enhancement in aqueous solubility upon cyclodextrin complexation (*see* paragraph 6, above).

(8) The solubility of modafinil in 50% aqueous 2-HP-β-cyclodextrin is at least 45 mg/mL, which corresponds to a relative solubility enhancement of 112.5 (45/0.4). Even at an aqueous solubility of 30 mg/mL, the relative solubility enhancement for modafinil is 75 (30/0.4). In my opinion, the large enhancement in the aqueous solubility of modafinil observed upon cyclodextrin complexation would not reasonably have been expected at the time of the present invention.

(9) I have studied the publication Pitha, J. et al., *Int. J. Pharm.*, **1986**, *29*, 73-82. In my opinion, Pitha discloses the use of HP-β-cyclodextrin to improve the aqueous solubility of several drugs. Table 1 of Pitha discloses the aqueous solubility of thirty (30) compounds alone and with added HP-β-cyclodextrin. As shown in the attached Table 1, eight (8) of these thirty (30) compounds have an aqueous solubility of at least 1.46 mmol/L (i.e., the aqueous solubility of modafinil). The eight (8) compounds are acetamidophen, apomorphine, iproniazid phosphate, nitroglycerin, norethindrone, oubain, oxprenolol, and theophylline. Significantly, *none* of these eight (8) compounds exhibited a relative solubility enhancement factor of 75 or more when mixed with 2-HP-β-cyclodextrin.

(10) Nine (9) additional compounds from Pitha's Table 1 have a water solubility within an order of magnitude lower than modafinil (i.e., 146 μmol/L to 1.46 mmol/L). The nine

(9) compounds are cholecalciferol, dexamethasone, dicumarol, furosemide, hydroflumethiazide, 17-methyltestosterone, retinal, retinoic acid, and sulpiride. Only three (3) of these nine (9) compounds exhibited a relative solubility enhancement factor of 75 or more when mixed with HP-β-cyclodextrin.

(11) In my opinion, Pitha would not provide a person of ordinary skill in the art with a reasonable expectation that HP-β-cyclodextrin would enhance the aqueous solubility of modafinil to 30 mg/mL (i.e., a relative solubility enhancement factor of 75). My opinion is based on the teaching of:

(a) Loftsson that large enhancements in aqueous solubility upon cyclodextrin complexation maybe predicted only for drugs that have a starting aqueous solubility in the micromole/L range (or lower),

(b) Pitha that *none* of the eight (8) compounds having an aqueous solubility as high as modafinil had a relative solubility enhancement factor as high as modafinil, and

(c) Pitha that only three (3) of the nine (9) less relevant compounds having an aqueous solubility within an order of magnitude lower than modafinil had a relative solubility enhancement factor as high as modafinil.

(12) I have studied the publication Loftsson, T., *Pharm. Tech.*, **1999**, *12*, 40-50. In my opinion, Loftsson recognizes that cyclodextrins can increase bioavailability, but cautions that the situation is complicated because cyclodextrins are also known to decrease bioavailability.

(13) I have studied the publication Hostetler, J.S. et al., *Antimicrob. Agents Chemother.*, **1992**, *36*, 477-480. In my opinion, Hostetler shows that complexation with HP-β-cyclodextrin sometimes significantly increases drug absorption (itraconazole, saperconazole), but sometimes increases absorption very little (ketoconazole) or not at all (fluconazole, miconazole, SCH 42427).

(14) I have studied the publication Nakanishi et al., *Chem. Pharm. Bull.*, **1989**, *37*, 211-214. In my opinion, Nakanishi shows that cyclodextrin complexation can sometimes decrease drug absorption (sulfamethizole, cinnarizine).

(15) I have studied the abstract of the publication Spirichev et al., *Vopr. Pitan.*, **1996**, *6*, 22-26. In my opinion, Spirichev shows that cyclodextrin complexation can sometimes decrease drug absorption (beta-carotene).

(16) I am generally familiar with the literature relating to drug complexation with cyclodextrins. In my opinion, at the time of the present invention published reports of cyclodextrin complexation improving drug bioavailability were counterbalanced by published reports such as Loftsson, Hostetler, Nakanishi, and Spirichev in which the rate and extent of drug absorption was either not improved or even worsened. Consequently, at the time of the present invention it was not predictable whether cyclodextrin complexation would improve the bioavailability of a drug.

(17) I am a co-inventor of the subject matter disclosed in U.S. Patent No. 6,489,363 ('363 patent), entitled "Pharmaceutical solutions of modafinil compounds." Example 1 of the '363 patent describes the preparation of a pharmaceutical solution of modafinil dissolved in a mixture of PEG-400 and benzyl alcohol (95:5 (v/v)). The solubility of modafinil in the solution was 61 mg/mL. Example 2 of the '363 patent describes the blood serum levels of modafinil observed after oral administration of the PEG-400:benzyl alcohol solution to rats.

(18) The attached Table 2 and Figure 1 show the modafinil blood serum levels observed in rats after oral administration of (a) the PEG-400:benzyl alcohol solution of the '363 patent, (b) the Oraplus® suspension of the '363 patent, and (c) the 2-HP-β-cyclodextrin solution of the present application (Examples 1 and 3). The attached Table 3 shows the pharmacokinetic data calculated for each dosage form.

(19) As shown in Table 3, the area under the modafinil concentration curve (AUC_{0-6}, μg·hr/mL) was 4.6 times higher for the 2-HP-β-cyclodextrin solution as compared to the Oraplus® suspension (40.525/8.869) and 5.9 times higher for the 2-HP-β-cyclodextrin solution as compared to the PEG400:benzyl alcohol solution (40.525/6.918). In other words, the extent of modafinil absorption from the cyclodextrin solution was 4.6 times higher than the Oraplus® suspension and 5.9 times higher than the PEG400:benzyl alcohol solution.

(20) As shown in Table 3, the maximum modafinil blood concentration (C_{max}, μg/mL) was 4.5 times higher for the 2-HP-β-cyclodextrin solution as compared to the Oraplus® suspension (22.110/4.917) and 6.9 times higher for the 2-HP-β-cyclodextrin solution as compared to the PEG400:benzyl alcohol solution (22.110/3.197).

(21) As shown in Table 3, the time of highest modafinil blood concentration (t_{max}, μg/mL) was similar for all three (3) dosage forms (i.e., 0.500 to 0.667 hours). In other words, the rate of modafinil absorption from the cyclodextrin solution was not substantially slower than from the Oraplus® suspension or the PEG400:benzyl alcohol solution. This is important because it indicates that the modafinil was suitably released from the modafinil:cyclodextrin complex.

(22) In my opinion, it was not predictable at the time of the present invention that complexation of a modafinil compound with a cyclodextrin would substantially increase its extent of absorption without substantially decreasing its rate of absorption, especially as compared to a true modafinil solution in PEG400:benzyl alcohol. Accordingly, the oral bioavailability of the modafinil:cyclodextrin complex as set forth in paragraphs 18-21 constitutes an unexpected result. My opinion is based on my own experience with cyclodextrin complexation and the state of the published literature at the time of the present invention (*see* paragraph 16, above).

(23) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: January 19, 2006

Martin J. Jacobs

Table 1. Aqueous Drug Solubilities (from Pitha Table 1)

Drug	Aqueous Solubility (mg/mL)	Aqueous Solubility with HP-β-Cd (mg/mL)	Relative Solubility Enhancement	Molecular Weight (g/mol)	Aqueous Solubility (mmol/L)
acetamidophen	11	67	6.09	151	72.8
apomorphine	20	116	5.8	267	74.9
butylated hydroxytoluene	0.01	3	300	164	0.061
chlorthalidone	0.12	10.5	87.5	339	0.35
cholecalciferol	0.23	10	43.5	385	0.60
dexamethasone	0.1	24	240	392	0.26
dicumarol	0.15	1.3	8.67	336	0.45
digoxin	0.07	68	971.4	781	0.090
diphenylhydantoin	0.03	1.7	56.7	252	0.12
estradiol	0.004	28	7000	272	0.015
estriol	0.003	41	13670	288	0.010
ethinylestradiol-3-methyl ether	0.01	27	2700	310	0.032
ethisterone	0.0006	0.5	833.3	312	0.0019
furosemide	0.07	1.7	24.3	331	0.21
hydroflumethiazide	0.3	9.3	31	331	0.91
indomethacin	0.02	4.2	210	434	0.046
iproniazid phosphate	30	95	3.17	277	108.3
17-methyltestosterone	0.17	39	229.4	302	0.56
nitroglycerin	1.25	10.4	8.32	227	5.5
norethindrone	2.5	6.8	2.72	298	8.4
oubain	13	80	6.15	585	22.2
oxprenolol	127	238	1.87	265	479.2
progesterone	0.015	34	2270	314	0.048
retinal	0.07	2.6	37.1	284	0.25
retinoic acid, all trans	0.07	0.8	11.4	300	0.23
retinol	0.01	5.5	550	286	0.035
spironolactone	0.03	42	1400	417	0.072
sulpiride	0.21	10	47.6	341	0.62
testosterone	0.026	38	1460	288	0.090
theophylline	8.3	11	1.33	180	46.1
modafinil	0.4	30	75	273.35	1.46

Table 2. Blood Serum Levels of Modafinil in Rats (μg/mL)

TIME (Hrs.)	PEG-400:Benzyl Alcohol (95:5 (v/v))	Oraplus®	2-HP-β-Cyclodextrin
0.25	2.4	3.4	11.65
0.5	1.4	4.9	21.3
1	1.4	3.0	19.7
2	1.2	1.9	7.1
4	1.2	0.4	1.8
6	0.5	0.2	0.5

Figure 1. Blood Serum Levels of Modafinil in Rats (μg/mL)

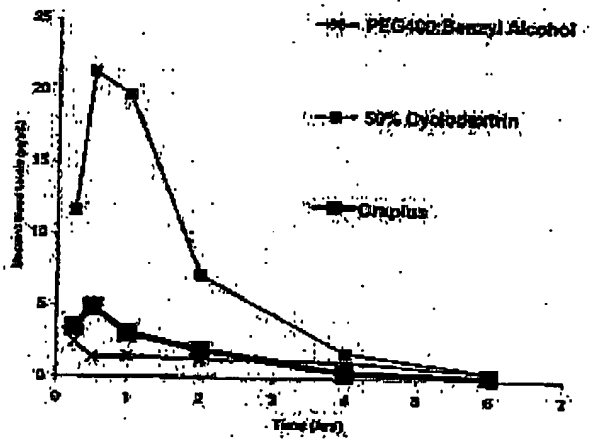

Table 3. Pharmacokinetic Results for Modafinil Oral Dosage Forms

	PEG-400:Benzyl Alcohol (95:5 (v/v))	Oraplus®	2-HP-β-Cyclodextrin
AUC_{0-6} (μg-hr/mL)	6.918	8.869	40.525
$t_{1/2}$ (hr)	2.941	1.183	1.198
t_{max} (hr)	0.583	0.500	0.667
C_{max} (μg/mL)	3.197	4.917	22.110